Complete Summary

GUIDELINE TITLE

Gliadel wafers in the treatment of malignant glioma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Perry J, Chambers A, Spithoff K, Laperriere N, Neuro-oncology Disease Site Group. Gliadel wafers in the treatment of malignant glioma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Aug 15. 19 p. (Evidence-based series; no. 9-7). [12 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Newly diagnosed or recurrent malignant glioma (i.e., glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Neurology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the safety and efficacy of Gliadel® (interstitial chemotherapy with carmustine-loaded polymers) in the treatment of newly diagnosed or recurrent malignant glioma (i.e., glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma)

TARGET POPULATION

Adult patients undergoing surgery for newly diagnosed or recurrent malignant glioma

INTERVENTIONS AND PRACTICES CONSIDERED

Gliadel® (interstitial chemotherapy with carmustine-loaded polymers)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1990 to March 2006, week 3), EMBASE (1990 to 2006, week 11), CANCERLIT (1990 to October 2002), and the Cochrane Library (2006, Issue 1) were searched. The terms "glioma" (Medical subject heading [MeSH]) and "brain neoplasms" were combined with the text words "Gliadel", "carmustine" and "BCNU". In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/clinical_trials/) and the proceedings of the

1997 to 2005 meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists from these sources were searched for additional trials.

Study Inclusion Criteria

Articles were selected for inclusion if they:

1. Were fully published reports of randomized controlled trials (RCTs) comparing treatment with Gliadel® wafers to placebo or alternative treatment in patients with malignant glioma. Prospective cohort studies were also included.
2. Included results regarding the safety or efficacy (i.e., survival) of Gliadel®.

Study Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.

NUMBER OF SOURCE DOCUMENTS

Four articles were included

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The Disease Site Group (DSG) decided not to pool the two randomized controlled trials (RCTs) that included patients with newly diagnosed malignant glioma because of the methodological limitations of the smaller trial. Only 16 patients were included in each arm of the trial and there were imbalances in key prognostic factors such as tumour histology and performance status between treatment groups. The Disease Site Group did not believe that pooling data from the trials of newly diagnosed malignant glioma with the trial of recurrent malignant glioma was reasonable due to the clinical heterogeneity between these patient groups.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Newly Diagnosed Malignant Glioma

Two randomized controlled trials (RCTs) compared the efficacy of Gliadel® versus placebo in patients with newly diagnosed gliomas. In the largest RCT to date, a two-month improvement in median survival for patients with newly diagnosed malignant glioma receiving Gliadel® compared to patients who received a placebo was reported (p=0.017). In addition, the analysis of the survival curves revealed a significant 27% reduction in risk of mortality for patients who received Gliadel® (p=0.018). A survival advantage of Gliadel® for patients with glioblastoma multiforme (GBM) was not detected, although the trial was not designed to make comparisons between histological subgroups. Another randomized trial only included 32 patients newly diagnosed with malignant glioma, because the researchers were unable to obtain Gliadel® during the trial. While a survival benefit was reported for Gliadel® in the entire patient population and for patients with GBM, no conclusions could be reached based on this small number of patients.

Both studies reported similar adverse effects in the treatment and control arms. The most common adverse effects associated with Gliadel® were hemiplegia, convulsions, confusion, and brain edema. The most commonly reported adverse effects among patients receiving the placebo were convulsions, confusion, brain edema, and aphasia. A significantly higher number of patients experienced intracranial hypertension in the Gliadel® arm of the Westphal trial. Since neither trial included a comparison with systemic therapy, it is unclear how the adverse effect rates associated with interstitial chemotherapy wafers compares to the rates expected with systemic chemotherapy.

As the largest trial does demonstrate a survival advantage in the Gliadel® treatment arm, Gliadel® may be considered an option in the subgroup of patients with newly diagnosed resectable malignant gliomas. However, the patient population (based on age, histology, performance status, etc.) that would benefit from Gliadel® is unclear and needs to be further investigated. In addition, no comparison has been performed between the efficacy of interstitial and systemic chemotherapy; therefore, clinicians should review the latest evidence for the benefit of systemic chemotherapy in patients with newly diagnosed malignant glioma. (See Practice Guideline #9-2 *Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma*).

Recurrent Malignant Glioma

One RCT compared the efficacy of Gliadel® versus placebo in patients with recurrent gliomas. The overall result of that trial was negative, with no significant survival advantage seen in the primary analysis; however, a survival advantage for Gliadel® in the entire patient population and in patients with GBM was observed after the adjustment for prognostic factors. As there were no *a priori* subgroups identified, the results of the subgroup analysis of GBM patients should

be interpreted with caution. While no survival advantage for Gliadel® was detected in the cohort study with historical control, no conclusions can be reached due to the heterogeneity between patients and potential for bias in such studies. The positive results of the RCT after the adjustment for prognostic factors suggest that Gliadel® may increase overall survival in some patients with recurrent resectable malignant glioma. Since those patients generally have a poor outlook, any treatment that has the potential for prolonging life without significant adverse effects should be considered as an option.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Report Approval Panel

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series and review and approval of the report by the Program in Evidence-based Care Report Approval Panel, the Neuro-oncology Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through an electronic survey of 55 practitioners in Ontario (medical oncologists, radiation oncologists, neurologists and neurosurgeons). The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was emailed on June 22, 2006. Follow-up reminders were sent on July 21 and August 4, 2006. The Neuro-oncology Disease Site Group reviewed the results of the survey.

This report reflects the integration of feedback obtained from the Report Approval Panel of the Program in Evidence-based Care and through the external review process, with final approval given by the Neuro-oncology Disease Site Group.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Gliadel®, followed by standard radiotherapy, is an option for selected patients with newly diagnosed malignant glioma where a near-gross total excision is possible; however, the majority of patients with malignant glioma will not be eligible for various reasons (i.e. non-resectable tumours or contact with the ventricular system).
- The current standard of care for patients with newly diagnosed glioblastoma multiforme is radiotherapy with concurrent and adjuvant temozolomide. No evidence is currently available to support the sequential combination of Gliadel® with temozolomide; however, the Disease Site Group (DSG) does not feel that the placement of Gliadel® should preclude the administration of systemic therapy. Decisions to use Gliadel® with subsequent temozolomide should be made on an individual patient basis, recognizing that there is little clinical experience with such combined treatment, and patients should be made aware of the possibility of increased toxicity. When new evidence becomes available, the Disease Site Group (DSG) will revise these recommendations as necessary.
- Gliadel® is an option in patients with surgically resectable recurrent malignant gliomas.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and a cohort study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Newly Diagnosed Malignant Glioma

- One randomized controlled trial (RCT) of newly diagnosed malignant glioma reported a significant improvement in median overall survival in patients who received Gliadel® compared to those who received the placebo (13.8 months in the Gliadel® arm versus [vs.] 11.6 months in the placebo arm, p=0.017). The estimated mortality hazard ratio for Gliadel® compared to control was 0.73 (95% confidence interval 0.56-0.95, p=0.018), representing a 27%

decrease in risk of death over the course of the study for patients who received Gliadel®. There was no statistically significant difference in one-year overall survival or progression-free survival between the two treatment arms.
- Another RCT was limited to only 32 patients newly diagnosed with malignant glioma, because halfway through the trial the researchers were unable to obtain Gliadel®.

Recurrent Malignant Glioma

- One RCT compared Gliadel® to placebo in patients with recurrent malignant glioma. Median survival was 7.2 months in the Gliadel® arm compared to 5.3 in the placebo arm; however, six month overall survival was not significantly different (60% in the Gliadel® arm and 47% in the placebo arm, p=0.061).
- A cohort study reported a survival benefit in favour of patients who did not receive Gliadel®; however, this study was affected by selection bias and used a retrospectively-identified control cohort.

POTENTIAL HARMS

All of the studies reported similar adverse effects in the treatment and control arms. The most common adverse effects associated with Gliadel® were hemiplegia, convulsions, confusion, and brain edema. The most commonly reported adverse effects among patients receiving the placebo were convulsions, confusion, brain edema, and aphasia. The largest randomized controlled trial (RCT) of 240 patients reported a greater occurrence of intracranial hypertension in patients who received Gliadel® compared to those who received placebo (9.2% vs. 1.7%, p=0.019).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The patient population (based on age, histology, performance status, etc.) that would benefit from Gliadel® is unclear and needs to be further investigated.
- There is no evidence available comparing the efficacy of Gliadel® to systemic chemotherapy, therefore no comment can be made regarding the relative efficacy of Gliadel® compared to alternative treatment options. For recommendations of adjuvant systemic chemotherapy for newly diagnosed malignant glioma, refer to Evidence-based Series #9-2.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Perry J, Chambers A, Spithoff K, Laperriere N, Neuro-oncology Disease Site Group. Gliadel wafers in the treatment of malignant glioma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Aug 15. 19 p. (Evidence-based series; no. 9-7). [12 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Aug 15

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Neuro-Oncology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Neuro-Oncology Disease Site Group (DSG) were polled for conflicts of interest relating to the topic of this systematic review and meta-analysis. No conflicts were declared.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Gliadel wafers in the treatment of malignant glioma: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Aug. Various p. (Practice guideline; no. 9-7). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI Institute on June 4, 2007. The information was verified by the guideline developer on June 13, 2007.

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